Systematic Review of Ovarian Activity and Potential for Embryo Formation and Loss during the Use of Hormonal Contraception

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Abstract

The purpose of this review was to determine whether there is evidence that ovulation can occur in women using hormonal contraceptives and whether these drugs might inhibit implantation. We performed a systematic review of the published English-language literature from 1990 to the present which included studies on the hormonal milieu following egg release in women using any hormonal contraceptive method. High circulating estrogens and progestins in the follicular phase appear to induce dysfunctional ovulation, where follicular rupture occurs but is followed by low or absent corpus luteum production of progesterone. Hoogland scoring of ovulatory activity may inadvertently obscure the reality of ovum release by limiting the term “ovulation” to those instances where follicular rupture is followed by production of a threshold level of luteal progesterone, sufficient to sustain fertilization, implantation, and the end point of a positive β -human chorionic gonadotropin. However, follicular ruptures and egg release with subsequent low progesterone output have been documented in women using hormonal contraception. In the absence of specific ovulation and fertilization markers, follicular rupture should be considered the best marker for egg release and potential fertilization. Women using hormonal contraceptives may produce more eggs than previously described by established criteria; moreover, suboptimal luteal progesterone production may be more likely than previously acknowledged, which may contribute to embryo loss. This information should be included in informed consent for women who are considering the use of hormonal contraception.

Summary: For this study, the authors looked at English-language research articles that focused on how hormonal birth control, such as the birth control pill, may affect very early human embryos. The authors found that abnormal ovulation, or release of an egg followed by abnormal hormone levels, may often occur in women using hormonal birth control. This may increase the number of very early human embryos who are lost before a pregnancy test becomes positive. For women who are thinking about using hormonal birth control, this is important information to consider.

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Introduction

Hormonal contraception has been used for over fifty years, in various doses and routes of administration, to prevent pregnancy (pregnancy is recognized when there is a positive serum or urine β -human chorionic gonadotropin [hCG] at the end of a woman's menstrual cycle). The high doses of estrogens originally used in hormonal contraception in the 1960s have been dramatically reduced due to concerns for thrombotic and vascular complications (Bitzer and Simon 2011). These lower ethinyl estradiol dosages are less effective at suppressing ovarian follicular activity. However, efficacy, defined using the end point of the absence of a positive pregnancy test at the end of the menstrual cycle, has not been noted to significantly change as ethinyl estradiol dosages have decreased (Bitzer and Simon 2011).

For medical professionals and patients who do not consider the embryo to be a human being, the absence of a positive pregnancy test at the end of a menstrual cycle is a useful end point to measure contraceptive efficacy, and the means by which this occurs is incidental. However, for patients and medical professionals who believe that human life begins at fertilization, it is extremely important to define whether a contraceptive method allows for the possibility of fertilization. If no ovum is released from the Graafian follicle, then fertilization and embryo formation are not possible. However, if follicular rupture and ovum release occur, then embryo formation is possible, and whether the environment facing the embryo is conducive to survival or not, becomes an important question.

To date, contraceptive researchers have not investigated contraceptives' postfertilization mechanisms of action, although such mechanisms are tacitly acknowledged as adding to contraceptive efficacy (ESHRE Capri Workshop Group 2001; Benagiano, Pera, and Primiero 2000; Puri et al. 2000; Katkam et al. 1995). Yet postfertilization mechanisms of action should be presumed in situations where egg release is not prevented. The end point for defining whether ovulation has occurred during use of hormonal contraception has been detection of a positive pregnancy test at the end of a menstrual cycle rather than by detection of ovum release by the Graafian follicle. This has led to

confusing and inconsistent definitions of ovulatory activity as noted in a systematic review by van Heusden, Coelingh Bennink, and Fauser (2002). This situation persists to date.

The advent of the Hoogland scoring system (Hoogland and Skouby 1993) has contributed some standardization to descriptions of ovulatory activity, thus allowing for comparison between studies over the past fifteen years. However, Hoogland scoring defines ovulation as having occurred with both follicular rupture on ultrasound plus a threshold midluteal progesterone level, implicitly defining as "nonovulation" those follicular ruptures with egg release where the subsequent midluteal progesterone level is low. Yet such follicular ruptures are precisely the ovarian activity of concern to the patient and practitioner who want to avoid contraceptives with embryocidal postfertilization mechanisms of action because use of these contraceptives may allow embryo formation, subsequent deficient support of the early embryo, and embryonic loss.

To clarify the types of ovarian activity that occur with the use of hormonal contraceptives, a reevaluation of current terminology as well as a summary of data on ovarian activity during the use of various hormonal contraceptives will aid in delineating future research efforts in this subject.

The Limits of Currently Used Terminology Describing Ovarian Activity

Proxy markers of ovulation. Ovulation is defined as the release of the secondary oocyte from the Graafian follicle (Medical Dictionary 2012). Currently, there are no definitive, unambiguous markers for ovulation *in vivo*. There are two biochemical markers (β -hCG and midluteal progesterone) and two anatomic markers (direct visualization of stigmata of ovulation and serial sonographic visualization of follicular rupture), which have been proposed as proxy markers for ovulation. Each of these proxy markers has certain limitations, including false-positive and false-negative rates. These are important to understand in order to quantify whether egg release has occurred with the use of hormonal contraception, and therefore, whether embryo formation may have occurred. The proxy markers and their limitations are discussed below.

β -hCG, a marker for embryo implantation. The embryo produces hCG from the trophoblast at clinically detectable levels after implantation. For embryos to form, egg release must have taken place. The presence of pregnancy-related hCG can be confirmed by detection of its β subunit at a level over 14 mIU/mL (Goldstein et al. 2016). False positives can occur, since β -hCG can also be elaborated in paraneoplastic syndromes and by the pituitary in perior postmenopausal women, as well as in molar pregnancies (Goldstein et al. 2016). False negatives can also occur, as absence of β -hCG does not rule out the possibility of ovulation and embryo formation with subsequent demise prior to implantation.

Threshold progesterone level, a marker for normal ovulation. Progesterone is produced by the granulosa cells of the Graafian follicle which have been stimulated (luteinized) by luteinizing hormone (LH). Historically, measurement of midluteal progesterone was used as an indication of corpus luteum formation and thus a biomarker for presumed ovulation.

Landgren, Unden, and Diczfalussy (1980) proposed the use of a threshold progesterone level as a marker for ovulation in contraceptive research. These authors assumed "ovulation" had occurred if an LH peak could be detected and subsequently measured progesterone values relative to the LH peak. In sixty-eight normal women, all had plasma progesterone levels >13 nmol/L at some point during the luteal phase. This study did not, however, correlate the luteal-phase progesterone level with other markers of ovulation. Subsequently, various threshold progesterone levels have been used by researchers to attempt to define ovulation. Some of these cutoffs were derived from in vitro fertilization (IVF) research on patients with unexplained infertility. The end point of the IVF research was to determine what the optimal progesterone levels might be, which are associated with the highest likelihood of embryo survival after transfer. (See discussion of dysfunctional ovulation below.) However, lack of an optimal progesterone level in the luteal phase (a level associated with better embryo survival) does not rule out ovulation. Instead, it only suggests that embryos do not survive as well at subthreshold luteal progesterone levels. The studies used to define the various progesterone thresholds did not correlate luteal progesterone levels with documented egg release, and in fact, subsequent studies disprove the assumption that egg release cannot occur with low luteal-phase progesterone levels. For example, Birtch, Olatunbosun, and Pierson (2006) described an ultrasound-verified ovulation associated with a progesterone of

0.79 ng/mL six days later. "The follicle that ovulated in the 30 ugEE/150 ug LNG conventional administration group had no detectable estradiol output for the 7 days prior to its ovulation. A CL [corpus luteum] was visualized ultrasonographically, and the serum progesterone level observed on Day 6 post-ovulation was 0.79 ng/mL [2.51 nmol/L]" (p. 239)

Similarly, Croxatto et al. (1998) found that five out of nine studied cycles demonstrated follicular rupture but would be considered anovulatory based on "endocrine criteria for ovulation" such as luteal progesterone. In fact, the 1998 Croxatto et al. study cited clearly illustrates that two separate, independent processes are occurring: (1) follicular rupture and (2) subsequent progesterone production. Decreased progesterone production was present in over half of the ultrasound-documented follicular ruptures in this study. Further, Croxatto et al. state that when progesterone does not meet the cutoff chosen, those cycles with follicular rupture "are considered anovulatory."

Cycles with ultrasound-documented follicular rupture and suboptimal progesterone levels are often classified as anovulatory in the contraceptive literature based on arbitrary progesterone cutoffs. Admittedly, it is not clear whether follicular rupture should be equated with ovulation. It is possible that eggs may be retained in follicles which rupture in association with poor progesterone elaboration, although there is no evidence for this. However, there is also no proof of the opposite hypothesis: that during a menstrual cycle with documented follicular rupture and suboptimal progesterone, an egg cannot possibly have been released.

Direct visualization of the "stigma of ovulation" by laparoscopy or laparotomy, a marker for ovulation. The release of the ovum from the Graafian follicle results in a reddened, convoluted mark on the surface of the ovary (Shaw 1927) known historically as the stigma of ovulation. Direct visualization of the stigma of ovulation was the historical "gold standard" for detection of ovulation prior to ultrasound, and visualization of stigma of ovulation confirmed ovulation.

However, the inverse was not found to hold true, as there appeared to be false negatives for detection of stigma of ovulation. After Stein and Levanthal (1935) postulated a theory of "luteinized unruptured follicles" (LUFs) as a reason for unexplained infertility, other researchers reported the absence of stigma of ovulation at the time of laparoscopy for infertility.

D'Hooghe et al. (1996), in research on LUFs, attempted to correlate presence of the stigma of ovulation with actual egg release. The authors reported

on 138 laparoscopies in baboons where the ovaries were examined for stigma of ovulation. The fallopian tubes and uteri were then flushed, and the effluent examined to identify eggs and embryos. The authors recovered eggs in 13 percent of cycles without a visible ovarian stigma at the time of laparoscopy. In a review of LUFs in humans, Katz (1988) cited a study documenting pregnancies which occurred after laparoscopies in cycles without stigmata of ovulation. D'Hooghe et al.'s recovery of eggs in 13 percent of cycles without stigma of ovulation and Katz's cases of pregnancy demonstrate that the absence of visible stigmata of ovulation cannot rule out egg release and subsequent embryo formation.

Ultrasound visualization of follicular rupture, a marker for ovulation. With the advent of ultrasound, the gold standard for ovulation detection moved from laparoscopic visualization of the stigma of ovulation to serial ultrasound documentation of follicular rupture. Arbitrarily, a 50 percent decrease in follicle size was referred to as "follicular rupture."

However, just as with previous proxy markers for ovulation (visualization of stigma of ovulation or threshold progesterone levels), this sonographic criterion for ovulation has never been definitively correlated with actual egg release. Further, whether or not the sonographic criterion is met is dependent on the frequency of scanning, the timing of serial scanning, and the skill of the sonographer. If the dominant follicle is not captured at peak size, the follicle might be read as having undergone shrinkage of less than 50 percent, and would fail to qualify as a follicular rupture, thus arbitrarily ruling out ovulation.

Liukkonen et al. (1984) investigated twenty-five patients who did not meet ultrasound criteria for follicular rupture and were therefore diagnosed with a LUF by ultrasound. However, at the time of laparoscopy, three of the cases (12 percent) diagnosed as an LUF by ultrasound had ovulation stigmata present. This suggests that ultrasound visualization of follicular rupture is not a perfect test for ovulation.

Check et al. (1990) studied 220 patients and found that 56 patients did not meet ultrasound criteria for follicular collapse (5-mm decrease in size) but had some lesser degree of collapse which was labelled "indeterminate." This group, which did not meet ultrasound criteria for follicular rupture, had a 5.4 percent pregnancy rate, demonstrating unequivocally that even when ultrasound criteria for ovulation are not met, an egg can be released.

Thus, all of the current proxy criteria for detection of ovulation have an unspecified false-negative rate. Moreover, none of the proxy measures has been definitely correlated with egg release. Each has been demonstrated in some studies to miss actual egg release, and each has been correlated to a pregnancy rate greater than zero in cases not classified as ovulation. This is an important point to consider when evaluating studies of ovulation rates with hormonal contraceptives, which state that no ovulation occurred during the use of a particular method of contraception.

Detection of ovulation in contraceptive research. Despite the lack of correlation between proxy markers and documented egg release, contraceptive researchers have promulgated various criteria for determining whether ovulation has occurred in women using hormonal contraceptives. These criteria were created to retrospectively detect an ovulation which had resulted in a positive pregnancy test. As such, any egg release that does not result in a progesterone level reaching an optimal threshold is not classified as an ovulation. This definition semantically eliminates situations where eggs may be released and fertilized, and embryos created, with subsequent luteal-phase defects leading to embryo demise. Thus, the statement that "no ovulation" has occurred while a woman has been taking a particular type of hormonal contraceptive are more accurately stated as "no *normal* ovulation" has occurred. An examination of the Hoogland criteria for ovulation clearly illustrates this point, as well as what is termed "dysfunctional ovulation."

Hoogland criteria for ovulation. In an attempt to standardize the categorization of ovarian activity occurring with the use of hormonal contraceptives, as well as to "deal with the controversy over the increased incidence of ovarian cysts during the use of a low-dose pill," Hoogland and Skouby (1993) proposed a combination of proxy measures, both sonographic and endocrinologic, in order to identify which combination of these measures would most likely lead to a positive pregnancy test at the end of a cycle, that is, a contraceptive "failure." With this efficacy end point in mind, these authors labeled certain combinations of sonographic activity and hormone production as ovulation, "LUF," "active follicle-like structure (FLS)," "nonactive FLS," and "no activity" (see Table 1).

Hoogland terminology was not correlated with the strict definition of ovulation, which is the

Table 1. Hoogland Criteria for Ovarian Activity.

Hoogland "ovulation"	<p>All of the following are required:</p> <ol style="list-style-type: none"> 1. Dominant follicle > 13 mm diameter 2. Ultrasound documentation of a decrease in follicle size by 50% or more within two to four days. When this criterion is met, the event is titled "follicular rupture." 3. Serum estradiol (E) level > 0.1 nmol/L in follicular phase 4. Serum progesterone (P) level > 5 nmol/L in luteal phase
Hoogland luteinized unruptured follicle	<p>All of the following are required:</p> <ol style="list-style-type: none"> 1. Dominant follicle > 13 mm diameter 2. Ultrasound documentation of a decrease in follicle size by less than 50% or occurring not within two to four days or not occurring at all. This ultrasound finding is called "no follicular rupture" even if follicular rupture actually did occur but the decrease in size detected by ultrasound was less than "50%." (Criterion 2 distinguishes "Hoogland ovulation" from "Hoogland luteinized unruptured follicle.") 3. Serum estradiol (E) level > 0.1 nmol/L in follicular phase 4. Serum progesterone (P) level > 5 nmol/L in luteal phase
Hoogland active follicle-like structure	<p>All of the following are required:</p> <ol style="list-style-type: none"> 1. Dominant follicle > 13 mm diameter 2. Follicles may or may not rupture 3. Serum estradiol (E) level > 0.1 nmol/L in follicular phase 4. Serum progesterone (P) level < 5 nmol/L in luteal phase (Criterion 4 distinguishes "Active Follicle-like Structure" from "Hoogland Ovulation" or "Hoogland Luteinized Unruptured Follicle.")
Hoogland nonactive follicle-like structure	<p>All of the following are required:</p> <ol style="list-style-type: none"> 1. Dominant follicle > 13 mm diameter 2. Follicles may or may not rupture 3. Serum estradiol (E) level > 0.1 nmol/L in follicular phase 4. Serum progesterone (P) level, any level (Criteria 3 and 4 distinguish "Non-active Follicle-like Structure" from "Hoogland Ovulation" or "Hoogland Luteinized Unruptured Follicle" or "Active Follicle-like Structure.")

Note: The bold face emphasizes the concept which deviates from the expected definition.

release of an ovum from a Graafian follicle. Nor were these categorizations subsequently correlated with actual egg release. Notwithstanding, this terminology was rapidly adopted by many contraception researchers as being useful for ruling out ovulation during the use of hormonal contraceptives. This did not take into account concerns about possible mechanisms of action which could lead to embryo demise.

However, as noted by Check et al. (1990), Liukkonen et al. (1984), Croxatto et al. (1998), and Birtch, Olatunbosun, and Pierson (2006), the Hoogland criteria do not actually establish that egg release has or has not occurred. Not only are these categories a composite of imperfect proxy markers as described

above, but they leave many potential ovulatory events undefined and only categorize a small number of them as ovulation. All four of Hoogland's categories involve follicles over 13 mm in diameter. All four of these categories may include actual follicle rupture. The distinction between the Hoogland categories is dependent upon the endocrinological activity of the follicle, and the skill and timing of the sonographer. Despite these concerns about the limitations of Hoogland's categories as tools for accurate detection of normal and abnormal ovulation, many researchers have considered Hoogland criteria as providing definitive evidence that egg release did not occur during the use of a particular contraceptive.

Dysfunctional ovulation. Croxatto et al. (2004) define dysfunctional ovulation as “follicular rupture not preceded by an LH peak, or preceded by a blunted LH peak (<21 IU/L), or not followed by elevation of serum P over 12 nmol/L.” This definition could correspond to Hoogland classifications of “Hoogland ovulation,” “Hoogland LUF,” “Hoogland active FLS,” or even “Hoogland nonactive FLS.”

The impact of dysfunctional ovulation with low luteal progesterone production on embryo survival has been documented by multiple infertility researchers (Lawrenz et al. 2018; Devoto et al. 2009; Ozlu et al. 2012; Arce et al. 2011; Andersen and Andersen 2014; Kaur and Gupta 2016; Achache and Revel 2006). Although there is no current consensus on an absolute minimum level of midluteal progesterone needed for embryo survival, low levels of midluteal serum progesterone are associated with excess embryo loss (Arce et al. 2011). Andersen and Andersen (2014, p. 555) reviewed “original studies from Hull and coworkers who reported a mid-luteal-phase progesterone concentration of 30nmol/l as the lower limit for conception in natural menstrual cycles, whereas this concentration was raised by a factor of about 3 (ie approx. 90 nmole/l) in gonadotrophin-stimulated cycles.” Luteal-phase progesterone support is standard during IVF cycles to increase the implantation and survival rates of transferred embryos (American Society for Reproductive Medicine in collaboration with the Society for Reproductive Endocrinology and Infertility 2008).

During investigation of a combined oral contraceptive (OC) regimen, Arce et al. (2011) stratified live birth rate (LBR) by midluteal *progesterone* among women who conceived during ovulation induction. These authors found the following:

Midluteal <i>P</i>	(LBR percent)
<i>P</i> = 7.9–10 ng/mL	(LBR = 8 percent)
<i>P</i> > 10–15 ng/mL	(LBR = 15 percent)
<i>P</i> > 15–25 ng/mL	(LBR = 21 percent)
<i>P</i> > 25–40 ng/mL	(LBR = 29 percent)
<i>P</i> > 40 ng/mL	(LBR = 32 percent)

Note also that these midluteal progesterone levels are well above the threshold progesterone level described by Hoogland.

Since progesterone mediates most of the genomic changes in the endometrium that are obligatory for implantation and placentation (Lawrenz et al. 2018; Achache and Revel 2006; Riesewijk et al. 2003), inadequate or mistimed progesterone production leads to an endometrial environment which is less receptive and which decreases the likelihood

of embryo implantation and survival. Interference with progesterone-dependent blastocyst adhesion and other steroid-dependent changes which are markers for endometrial receptivity is a recognized mechanism for “an interceptive approach to prevent embryo implantation” (Riesewijk et al. 2003). Such interference could result either from the direct actions of progestins on the endometrium and/or disruption of the timing or amount of luteal progesterone in relationship to follicle rupture.

Since it is LH stimulation of granulosa cells which results in luteinization and subsequent progesterone production, the amount and timing of the LH surge is critically important to achieving sufficient progesterone production during the luteal phase. Follicular rupture with ovum release which has been triggered by a blunted LH peak would result in luteinization of fewer granulosa cells, in turn resulting in deficient postovulatory progesterone production.

Such induced luteal-phase deficiency can be observed during ovulation induction cycles, with subsequent early luteolysis (Fatemi et al. 2013; Tanus et al. 2017). The latter appears to be caused by supraphysiologic levels of estrogen and progesterone secreted by multiple stimulated follicles and not by β -hCG used to trigger ovulation (Tavaniotou and Devroey 2003; Lawrenz et al. 2018). Since hormonal contraceptives similarly induce supraphysiologic levels of estrogens and progestins in cycles with escape ovulation, luteolysis may occur in these cycles as well. Blunted LH secretion is characteristic of cycles studied during the use of various hormonal contraceptives (Endrikat et al. 2013; van Heusden, Coelingh Bennink, and Fauser 2002; Pierson et al. 2003; Seidman et al. 2015; Kroll et al. 2015).

Hoogland scoring of ovarian activity provides some empiric evidence of midluteal ovarian function in cycles where follicles of sufficient size for ovulation (>13 mm) are observed, that is, Hoogland scores of 3 through 6. This article reviews the existing literature on numeric Hoogland scoring in women documented to be ovulatory prior to treatment with hormonal contraceptives. The goal of this analysis is to estimate the frequency of luteal-phase endocrinological disruption, which might be sufficient to cause postfertilization effects and excess embryo loss, in women using hormonal contraception.

Materials and Methods

A systematic review of the medical literature for papers published in English, was performed in PubMed, Medline/Ovid, and Embase, using the terms listed in Box 1.

Box 1. Search Terms (*n* = number retrieved)

Ovulation and ultrasound and contraception (*n* = 169)
 Hoogland score and contraception (*n* = 13)
 Follicular rupture and contraception (*n* = 22)
 Oral contraceptive and ovulation and suppression (*n* = 670)
 Contraceptive suppression (*n* = 1,090)
 Contraceptive Hoogland (*n* = 23)
 Contraceptive ovulation (*n* = 4,807)
 Contraception Hoogland (*n* = 23)
 Injectable contraception ovulation (*n* = 526)
 Oral contraception ovulation (*n* = 2,709)
 Implant contraception ovulation (*n* = 245)
 Vaginal ring contraception ovulation (*n* = 603)
 Transdermal contraception ovulation (*n* = 51)
 Progestin contraception ovulation (*n* = 1,072)
 Emergency contraception ovulation (*n* = 212)

References from articles which were reviewed were screened to identify additional English-language papers not identified in the initial searches. Articles were abstracted by two board certified obstetrician/gynecologists. Original research papers which provided sonographic and endocrinological data on ovarian activity with the use of various hormonal contraceptives were identified. Articles included in the table (*N* = 17) are those which contained original research data in numerical form sufficient to create a Hoogland score for ovulatory activity of at least Hoogland scores 3–6 during menstrual cycles while women were using hormonal contraception.

An additional six articles (Duijkers, Klipping, et al. 2015; Archer et al. 2009; Heger-Mahn et al. 2004; Rible et al. 2009; Klipping et al. 2012; Waellnitz et al. 2016) were identified which reported Hoogland scoring as a bar graph, and the authors queried for numerical data. Three authors responded (Waellnitz, Schuett for Klipping et al. 2012, and Rible). Rible et al. was not included as the sonographic data were obtained from early follicular and late luteal phase rather than the peri-ovulatory period. Two studies were excluded for incomplete reporting of Hoogland scoring: Endrikat et al. (2013) reported only Hoogland scores 5 and 6. Heger-Mahn et al. (2004) reported only Hoogland scores 4–6. Data extraction from articles meeting inclusion criteria was performed by two of the authors and confirmed by all authors. Results are reported in Table 2. One study (Westhoff et al. 2010) used a single data set, but data were analyzed in two different ways noted in Table 2 as Westhoff A and Westhoff B.

Articles which did not contain sufficient information for Hoogland scoring of ovarian activity, but which reported on luteal-phase endocrine function after sonographic documentation of follicular rupture were reviewed for information but not included in Table 2.

Results

Table 2 shows degrees of disruption of normal ovulation during the use of various hormonal contraceptives. Follicular rupture with a 50 percent decrease in follicle size captured by ultrasound, combined with a serum estradiol production greater than 0.1 nmol/L in the follicular phase and also a midluteal progesterone production above 5 nmol/L in the luteal phase (Hoogland ovulation) occurs less than 5 percent of the time on any of the formulations analyzed in the spreadsheet.

It is noteworthy that the most commonly observed ovarian activity recorded in the studies is 13 mm or larger follicles with adequate follicular estrogen production and subsequent inadequate luteal progesterone production (Hoogland active FLSs in 2–64.7 percent of cycles). Since follicle rupture can and does occur in the active FLSs category, this induced ovulatory dysfunction is the situation of greatest concern for embryo formation and excess embryo loss secondary to inadequate luteal progesterone production. The inadequate luteal-phase progesterone production documented with this type of ovarian activity leads to insufficient preparation of the endometrium for implantation, and inadequate support of the early pregnancy, leading to embryo loss.

Since Hoogland active FLSs are classified without regard to follicular rupture status, a numerical estimate of how often follicular rupture is followed by inadequate luteal progesterone occurs cannot be derived from Hoogland scoring in this article. However, several authors have documented follicular rupture during treatment cycles with hormonal contraceptives followed by inadequate luteal progesterone production:

- Duijkers et al. (2015, p. 425) note that “the single case in the drospirenone group with a Hoogland score of 6 had low progesterone concentrations indicating luteal insufficiency.”
- Ludicke et al. (2001, p. 245) report “in the one case graded as ovulation, an FLS of 34 mm diameter was detected on cycle day 11 in the third treatment cycle and measured 9

Table 2. Hoogland Score of Ovarian Activity during the Use of Various Hormonal Contraceptives.

Reference	Medication	Number of Cycles	Number of Follicles ≥ 13 mm (% Total)				Total Number of Follicles > 13 mm (%)
			Hoogland "Ovulation" (6)	Hoogland "LUF" (5)	Hoogland "Active FLS" (4)	Hoogland "Nonactive FLS" (3)	
			Foll. decrease by 50% Follicular phase E2 > 0.1 nmol/L L, E2 > 27,238 pg/mL Luteal phase P > 5 nmol/L	Foll. decrease by less than 50% Follicular phase E2 > 0.1 nmol/L L, E2 > 27,238 pg/mL Luteal phase P < 5 nmol/L	No criteria for decrease Follicular phase E2 > 0.1 nmol/L E2 > 27,238 pg/mL Luteal phase P < 5 nmol/L	No criteria for decrease Follicular phase E2 < 0.1 nmol/L E2 < 27,238 pg/mL No P criteria	
van der Does et al. (1995) ^a Combined cyclic pill triphasic	(1) Trignyon 30 µg EE/50 µg LNG, 40 µg EE/75 µg LNG, 30 µg EE/125 µg LNG	(1) 45 (2) 48; data from table 3	(1) 1/45 = 2.2% (2) 0/48 = 0% Note: follicle size > 15 mm	(1) 0/45 = 0% (2) 1/48 = 2.1% Note: follicle size > 15 mm	(1) 12/45 = 26.7% (2) 6/48 = 12.5% Note: follicle size > 15 mm	(1) 8/45 = 17.8%* (2) 3/45 = 6.7% size: >15 mm 3/45 10–15 mm 5/45	(1) 21/45 = 46.7%* (2) 17/48 = 35.4%**
	(2) 35 µg EE/50 µg DSG or 30 µg EE/100 µg DSG or 30 µg EE/150 µg DSG all classified as "EE/LNG"					(2) 10/48 = 20.8%*** size: >15 mm 4/48 10–15 mm 6/48	
Spona, Elstein, et al. (1996) Combined cyclic pill compare pill free interval	(1) 20 µg EE/75 µg GSD for twenty-one days	(1) 90 (2) 90	(1) 0/90 = 0% (2) 0/90 = 0%	(1) 0/90 = 0% (2) 0/90 = 0%	(1) 29/90 = 32.2% (2) 11/90 = 12.2%	(1) 5/90 = 5.6% (2) 4/90 = 4.4%	(1) 34/90 = 37.8% (2) 15/90 = 16.7%
	(2) 20 µg EE/75 µg GSD for twenty-three days						
Spona, Feichtinger, et al. (1996) ^b Combined cyclic pill	20 µg EE/100 µg LNG	71	0/71 = 0%	2/71 = 2.8%	21/71 = 29.6%	0/71 = 0%	23/71 = 32.4%
Rossmann, Steffens, and Schramm (1997) Combined cyclic pill Double blind RCT compare drug	(1) 20 µg EE/500 µg NET (Eve)	(1) Total cycles 172 (2) Total cycles 174; table 2	(1) 0/172 = 0% (2) 0/174 = 0%; table 2	(1) 1/172 = 1% (2) 0/174 = 0%; table 2	(1) 15/172 = 8.7% (2) 5/174 = 2.9%; table 2	(1) 2/172 = 1.2% (2) 2/174 = 1.1%; table 2	(1) 18/172 = 10.5% (2) 7/174 = 4.0%; table 2
	(2) 20 µg EE/150 µg DSG (Lovelie)						
Spona et al. (1997) Combined pill noncompare	30 µg EE/2 mg DNG	62 (table 3)	0/62 = 0%	4/62 = 6.5%	15/62 = 24.1%	2/62 = 3.2%	21/62 = 33.9%

(continued)

Table 2. (continued)

Reference	Medication	Number of Cycles	Number of Follicles ≥ 13 mm (% Total)				Total Number of Follicles > 13 mm (%)
			Hoogland "Ovulation" (6)	Hoogland "LUP" (5)	Hoogland "Active FLS" (4)	Hoogland "Nonactive FLS" (3)	
			Foll. decrease by 50% Follicular phase E2 > 0.1 nmol/L, E2 > 27.238 pg/mL Luteal phase P > 5 nmol/L	Foll. decrease by less than 50% Follicular phase E2 > 0.1 nmol/L, E2 > 27.238 pg/mL Luteal phase P > 5 nmol/L	No criteria for decrease Follicular phase E2 > 0.1 nmol/L, E2 > 27.238 pg/mL Luteal phase P < 5 nmol/L	No criteria for decrease Follicular phase E2 < 0.1 nmol/L, E2 < 27.238 pg/mL No P criteria	
Ludicke et al. (2001) ^c Combined cyclic pill open label non comparator	(1) 20 µg EE/50 µg GSD compared with control cycles with (20 EE/75 GSD) (2) Historical	(1) 63 (2) 52	(1) 1/63 = 1.58% (2) 0/52 = 0%	(1) 4/63 = 6.3% (2) 0/52 = 0%	(1) 19/63 = 30.15% (2) 20/52 = 39% *% from table 4	(1) 3/63 = 4.76% (2) 6/52 = 11%* *% from table 4	(1) 27/63 = 42.85% ^c (2) 26/52 = 50% from table 4
Endrikat et al. (2003) combined pill meta-analysis of various studies	Various	227; table 4 compiled	1/227 = 0.44%	2/227 = 0.88%	153/227 = 67.4%	23/227 = 10.1%	179/227 = 78.9%
Klipping et al (2008) Combined cyclic pill double blind RCT compare pill free interval	(1) 20 µg EE/3 mg DRSP 24 d ("24/4") (2) 20 µg EE/3 mg DRSP 21 d ("21/7")	(1) 98 cycles (2) 100 cycles	(1) 1/98 = 1.0% (2) 5/100 = 5.0%	(1) 0/98 = 0% (2) 1/100 = 1.0%	(1) 14/98 = 14.3% (2) 33/100 = 33.0%	(1) 0/98 = 0% (2) 0/100 = 0%	(1) 15/98 = 15.3% (2) 39/100 = 39.0%
Spona et al. (2010) combined pill observation Phase II	20 µg EE/2 mg Chlormadinone	88 table 3 "Medication cycles 1-3"	0/88 = 0%	1/88 = 1.1%	13/88 = 14.8%	1/88 = 1.1%	15/88 = 17.0%
Anzai et al. (2012)	20 µg EE + 3 µg DRSP (1) Japanese women (2) Caucasian women	(1) 36 (2) 46	(1) 0/36 = 0% (2) 2/46 = 4.3%	(1) 0/36 = 0% (2) 1/46 = -2.2%	(1) 6/36 = 16.7% (2) 5/46 = 10.9%	(1) 0/36 = 0% (2) 0/46 = 0%	(1) 6/36 = 16.7% (2) 8/46 = 17.4%
Klipping et al. (2012) POP continuous double blind RCT dose varies	DNG in four doses continued seventy-two days (1) 0.5 mg (2) 1 mg (3) 2 mg (4) 3 mg	(1) 42 (2) 46 (3) 40 (4) 46	(1) 3/42 = 7.1% (2) 2/46 = 4.3% (3) 0/40 = 0% (4) 0/46 = 0%	(1) 1/42 = 2.4% (2) 0/46 = 0% (3) 0/40 = 0% (4) 0/46 = 0%	Authors' data (1) 23/42 = 54.7% (2) 31/46 = 67.4% (3) 15/40 = 37.5% (4) 8/46 = 17.4%	Authors' data (1) 13/42 = 31.0% (2) 11/46 = 23.9% (3) 20/40 = 50.0% (4) 22/46 = 47.8%	Authors' data (1) 40/42 = 95.2% (2) 44/46 = 95.7% (3) 35/40 = 87.5% (4) 30/46 = 65.2%

(continued)

Table 2. (continued)

Reference	Medication	Number of Cycles	Number of Follicles ≥ 13 mm (% Total)				Total Number of Follicles > 13 mm (%)
			Hoogland "Ovulation" (6)	Hoogland "LUP" (5)	Hoogland "Active FLS" (4)	Hoogland "Nonactive FLS" (3)	
			Foll. decrease by 50% Follicular phase E2 > 0.1 nmol/L, E2 > 27.238 pg/mL	Foll. decrease by less than 50% Follicular phase E2 > 0.1 nmol/L, E2 > 27.238 pg/mL	No criteria for decrease Follicular phase E2 > 0.1 nmol/L, E2 > 27.238 pg/mL	No criteria for decrease Follicular phase E2 < 0.1 nmol/L, E2 < 27.238 pg/mL	
			Luteal phase $P > 5$ nmol/L	Luteal phase $P > 5$ nmol/L	Luteal phase $P < 5$ nmol/L	No P criteria	
Westhoff et al. (2014) Combined cyclic patch open-label uncontrolled phase 2b	0.55 mg EE/2.1 mg GSD cyclic three on one off BMI Groups (1) ≤ 30 (2) $> 30-35$ (3) > 35	(1) 99	table 3	table 3	table 3	table 3	table 3 data
		(2) 84	(1) 1/99 = 1.0% (2) 3/84 = 3.6% (3) 2/81 = 2.5%	(1) 0/99 = 0% (2) 3/84 = 3.6% (3) 1/81 = 1.2%	(1) 16/99 = 16.1% (2) 20/84 = 23.8% (3) 17/81 = 21.0%	(1) 0/99 = 0% (2) 1/84 = 1.2% (3) 0/81 = 0%	(1) 17/99 = 17.2% (2) 27/84 = 32.1% (3) 20/81 = 24.7%
		(3) 81					Data from table 4
Duijkers, Heger-Mahn, et al. (2015) POP regimen compare dose	(1) DRSP 4 mg $\times$ 24 d/mo (2) DSG 75 μ g $\times$ 28 d/mo (1) 20 μ g EE/150 μ g DSG + 7 d 10 μ g EE (2) 20 μ g EE/3 mg DRSP + 4 d placebo (3) 20 μ g EE/100 μ g LNG + 7 d placebo	(1) 54	(1) 1/54 = 1.9% (2) 1/58 = 1.7%	(1) 0/54 = 0% (2) 0/58 = 0%	(1) 23/54 = 42.6% (2) 35/58 = 60.3%	(1) 0/54 = 0% (2) 0/58 = 0%	(4) 18/102 = 17.6% (5) 29/95 = 30.5% (6) 20/84 = 23.8% (1) 24/54 = 44.4% (2) 36/58 = 62.1%
		(2) 58					
		105	3/105 = 2.86%	0/105 = 0%	9/105 = 8.57%	3/105 = 2.86%	15/105 = 14.29%
Seidman et al. (2015) Combined pill	(1) 0.55-mg EE/2.1-mg GSD; (2) 0.35-mg EE/0.67-mg GSD; (3) 0.275-mg EE/1.05-mg GSD	(1) 130	(1) 0/130 = 0% (2) 0/130 = 0% (3) 1/140 = 1%	(1) 0/130 = 0% (2) 2/130 = 1% (3) 0/140 = 0%	(1) 7/130 = 5% (2) 16/130 = 12% (3) 50/140 = 36%	(1) 4/130 = 3% (2) 1/130 = 1% (3) 3/140 = 2%	(1) 11/130 = 8.4% (2) 19/130 = 15% (3) 54/140 = 40%
		(2) 136					
		(3) 140					
Waelnitz et al. (2016) combined cyclic patch dose comparison		(1) 106	Authors data	Authors data	Authors data	Authors data	Authors data
		(2) 100	(1) 0/106 = 0% (2) 7/100 = 7.0% (3) 12/98 = 12.2%	(1) 0/106 = 0% (2) 3/100 = 3.0% (3) 2/98 = 2%	(1) 2/106 = 1.9% (2) 39/100 = 39.0% (3) 45/98 = 45.9%	(1) 2/106 = 1.9% (2) 2/100 = 2% (3) 4/98 = 4.1%	(1) 4/106 = 3.8% (2) 51/100 = 51.0% (3) 63/98 = 64.3%
		(3) 98					

(continued)

Table 2. (continued)

Reference	Medication	Number of Cycles	Number of Follicles ≥ 13 mm (% Total)				Total Number of Follicles > 13 mm (%)
			Hoogland "Ovulation" (6)	Hoogland "LUF" (5)	Hoogland "Active FLS" (4)	Hoogland "Nonactive FLS" (3)	
			Foll. decrease by 50% Follicular phase E2 > 0.1 nmol/L L, E2 $> 27,238$ pg/mL Luteal phase $P > 5$ nmol/L	Foll. decrease by less than 50% Follicular phase E2 > 0.1 nmol/L L, E2 $> 27,238$ pg/mL Luteal phase $P > 5$ nmol/L	No criteria for decrease Follicular phase E2 > 0.1 nmol/L E2 $> 27,238$ pg/mL Luteal phase $P < 5$ nmol/L	No criteria for decrease Follicular phase E2 < 0.1 nmol/L E2 $< 27,238$ pg/mL No P criteria	
Westhoff et al. (2010) ^d combined cyclic pill	(1) 20 µg EE/100 µg LNG	(1) 70	Combined results listed under Hoogland 5 in this spreadsheet	(1) 2/70 = 2.9%	(1) 16/70 = 22.9%	(1) 4/70 = 5.7%	(1) 22/70 = 31.4%
	(2) 30 µg EE/150 µg LNG	(2) 80		(2) 3/80 = 3.8% L	(2) 12/80 = 15.0%	(2) 8/80 = 10.0%	(2) 23/80 = 28.8%
	table 5 dose variation in consistent users			(1) 3/96 = 3.1%	(1) 1/96 = 1.0%	(1) 21/96 = 21.9%	(1) 31/96 = 32.3%
				(2) 1/54 = 1.9% Based on table 3 and text: "Three of the consistent OCP users who were normal weight and one was obese"	(2) 0/54 = 0% Based on tables 3 and 4 and text: "Three of the consistent OCP users who ovulated were normal weight and one was obese"	(2) 7/54 = 13.0%	(2) 14/54 = 25.9%

Note: EE = Ethinyl Estradiol; DSG = Desogestrel; LNG = Levonorgestrel; GSD = Gestodene; DRSP = Drospirenone; NET = Norethisterone; BMI = Body Mass Index.

^a"A trend toward increasing ovarian activity during longer treatment was found in both groups. This was not statistically significant."

^b"One volunteer exhibited progesterone serum levels of 3.6, 10.2, 5.7, and 6.0 ng/mL on cycle days 4,6,8, and 10, respectively, of treatment cycle 2. However, follicle diameters for this subject remained below 10 mm at all assessment times. Despite the fact that follicle-like structures did not exceed 10 mm, this was graded as LUF."

^cNote the sum of Hoogland 3-6 is 27 yielding a total 42.85%. This differs from table 4 and text reporting 62 percent of cycles with follicles greater than 13 mm.

^dOvulation rate (from table 3) consistent users 4/150 = 2.7%, inconsistent users 5/13 = 38.5%, all participants 21/181 = 11.6%. Deviations from Hoogland criteria: "Because of small numbers we combined grades 5 and 6" also note: p level used for inclusion was ≥ 3 ng/mL which equals >9.54 nmol/L instead of Hoogland > 5 nmol/L.

mm on cycle day 14. A maximum progesterone level of 10 ng/mL was found on Day 16.”

- Similarly, Birtch, Olatunbosun, and Pierson (2006, p. 239) reported “the follicle that ovulated in the 30 Ag EE/150 Ag LNG conventional administration group had no detectable estradiol output for the 7 days prior to its ovulation. A CL was visualized ultrasonographically, and the serum progesterone level observed on Day 6 postovulation was 0.79 ng/mL. The follicle that ovulated in the 35 Ag EE/250 Ag NGM group exhibited clinically normal serum estradiol concentrations during the preovulatory period. The progesterone level observed on Day 8 postovulation was 3.5 ng/mL.”

Of concern, Birtch, Olatunbosun, and Pierson also found persisting effects on corpus luteum function after discontinuation of an OC: “Clinically abnormal progesterone concentrations were observed following ovulation in approximately 40% of women following discontinuation of OC. Thus, reduced fertility following discontinuation of OC may be hypothesized to be due to luteal dysfunction following ovulation. This is only one possible explanation for the delay in fertility, and further investigations are required before a cause and effect relationship can be established.”

In studying the endocrinologic effects of a combined (norgestrel/ethinylestradiol) vaginal ring for emergency contraception, Croxatto et al. (2006) found a number of follicular ruptures not preceded by an LH peak within the previous twenty-four to forty-eight hours or preceded by a blunted LH peak (<21 IU/L) or not followed by elevation of progesterone over 12 nmol/L. These cases were defined as “ovulatory dysfunction,” and this was noted often.

Ovulatory dysfunction was observed in 31% (15/48) of ring cycles and in 6% (3/48) of control cycles ($p = .003$). The larger the follicle was at the time of ring insertion the higher was the frequency of ovulatory dysfunction. The percentage of ring-treated cycles presenting this condition increased from 13% to 50% for ring insertion at follicular size 12–14 and ≥ 18 mm, respectively (table 2). When limited to cycles with follicular rupture within the 5-day period, ovulatory dysfunction was observed in 15 (71%) of 21 ring cycles and in 3 (9%) of 32 control cycles ($p < .0001$). Croxatto et al. (2006)

Similarly, in an investigation of ovulatory activity during the use of a combined OC pill containing mifepristone followed by norgestrel acetate, Croxatto et al. (1998) noted follicular rupture in 30 percent of study cycles (nine of thirty). However, since five of those follicular ruptures had decreased progesterone production, these five cycles were “considered anovulatory” (termed “monophasic cycles”).

In cycles with documented follicular rupture and progesterone production meeting the threshold of ovulation (i.e., “biphasic cycles”), Croxatto et al. (1998) found altered LH secretion and significantly decreased progesterone concentrations ($p < .0072$) compared to controls:

The highest progesterone concentrations observed in each of the four ovulatory cycles (22.0 ± 4.9 nmol/l range 12.7–34.8) were also significantly below ($P = 0.04$) the range observed during their corresponding control cycles 37.4 ± 1.5 nmol/L range 35.3–41.8).

In those cycles, the endometrial morphology was also altered: The maximal endometrial thicknesses attained during the treatment cycles were lower than those observed during the baseline cycles, independent of the monophasic or biphasic profiles. Endometrial biopsies taken on days 7–10 of the third progestin treatment period showed disturbed development in all cases. All samples presented secretory signs but with a heterogeneous development of the glands... This glandular development was accompanied by dense stroma, with infrequent oedematous areas in most cases in which no vascular development or signs of focal predecidual reaction were observed... The most advanced development of the glands was always far ahead of the stroma and behind that required for the synchrony with the embryo.

Croxatto et al. (1998) also observed suppression of both endometrial growth and continued suppression of the LH surge, which persisted into the post-treatment period.

The likelihood that egg release from follicles greater than or equal to 13 mm could occur, combined with the large percentage of Hoogland active FLSs seen in women using all forms of hormonal contraceptives is cause for concern for embryo formation. In these situations, there is potentially a predisposition to embryo loss, due to (1) inadequate

priming of the endometrium, and/or (2) insufficient luteal-phase progesterone support for the embryo.

Discussion

Egg release is possible with the use of any method of contraception, as evidenced by pregnancy rates greater than zero for all contraceptive methods (Riviera, Yacobson, and Grimes 1999). The present study suggests, however, that follicular rupture followed by inadequate luteal-phase progesterone production with decreased embryo survival may be the most common scenario following follicular rupture and egg release.

In our review, ovulatory-sized follicles (>13 mm) with inadequate luteal-phase progesterone levels comprises the most commonly observed type of ovarian activity during the use of hormonal contraceptives (Hoogland 5, 4, 3; see Table 1). Each cycle characterized by these Hoogland criteria may include follicular rupture with ovum release, thus allowing for the possibility of fertilization and embryo formation. The use of Hoogland ovulation criteria is likely an effective paradigm for evaluating “contraceptive efficacy” since the end point of such efficacy is the likelihood of embryo survival and implantation, which results in a positive pregnancy test. However, Hoogland criteria cannot be used with any validity to evaluate how many embryos might be formed during a menstrual cycle with the use of a particular hormonal contraceptive.

In women not using hormonal contraceptives, biomarkers can help determine various levels of ovarian activity (Vigil et al. 2017). Blackwell, Cooke, and Brown (2018) suggest that luteal-phase deficiency may be distinguished from other ovarian activity by a peak of urinary estrone glucuronide followed by an increase in urinary pregnanediol glucuronide excretion rate exceeding 9 $\mu\text{mol}/24$ hours, but less than 13.5 $\mu\text{mol}/24$ hours. Further research would be needed in women using hormonal contraceptives who have documented follicular rupture, to determine whether or not estradiol and progesterone secretion patterns could be used to determine luteal-phase deficiency during the use of exogenous progestins.

Physiologically, the term “ovulation” means the release of an ovum from the Graafian follicle (Medical Dictionary 2012). However, by requiring a threshold luteal progesterone level to be present for categorization as Hoogland ovulation, Hoogland terminology itself precludes recognition of follicular rupture with subsequent luteal insufficiency, that is, ovum release and fertilization in the setting of

known luteal-phase defect. For this reason, Hoogland terminology to define ovulation cannot ensure that at least some embryos are not created. Arguments that a particular hormonal contraceptive does not allow for embryo formation, because no Hoogland ovulation was observed, are scientifically invalid because the existing published studies show that hormonal contraception is associated with luteal-phase disruption. The latter may account for the efficacy of hormonal contraceptives despite the frequency of follicular rupture and egg release.

While suboptimal luteal progesterone levels may contribute to contraceptive efficacy in view of likely follicular rupture, this induced luteal-phase defect is of concern to patients and medical professionals who regard the embryo as a human being and do not wish to use technology which may contribute to the death of embryonic human beings. The contraceptive failure rates, reported in the literature and cited to patients, represent embryos who have successfully implanted; they do not reflect how many embryos are formed and may be lost due to failure of implantation. As such, published failure rates represent a minimum number of embryos created during the use of that contraceptive drug or device.

The concept of “first do no harm” to patients is a major tenet of medical practice. The biological reality that a new human being is formed at fertilization leads to the conclusion that this tenet applies also to embryonic patients, both pre- and postimplantation. For practitioners, the important question is not only “How many embryos survived to the point of implantation and release of β -hCG (i.e., a positive pregnancy test)” but also “Is there evidence that embryos can be created, but lost due to the contraceptive prescribed, including those that did not survive to implantation release of β -hCG?”

Strengths and Weaknesses

This study appears to be the first systematic review of the contraceptive literature comparing the results of Hoogland scoring in multiple studies with various hormonal contraceptive formulations.

This study has weaknesses. One is the inability of Hoogland scoring to estimate the prevalence of egg release with the use of hormonal contraceptives due to the high false-negative rates of Hoogland criteria and the lack of correlation between Hoogland terminology and definitive measures of egg release. We are thus unable to arrive at an accurate estimate of ovulation rates, embryo survival rates, and/or embryo demise rates. To rule out the possibility of embryo formation with the use of hormonal

contraception requires that egg release be ruled out as well. As noted in the introduction, none of the current proxy criteria used for detection of ovulation has sufficient negative predictive value to be able to say with confidence that egg release has not occurred. The fact that documented follicular ruptures and egg releases may have occurred, even with deficient luteal progesterone, cannot rule out ovulation and embryo formation.

Further research is needed to identify and validate biomarkers for egg release with low false-negative rates and high positive predictive value. Such markers would need near 100 percent negative predictive value for ovulation to verify that a hormonal contraceptive works exclusively by prefertilization mechanisms of action. Fertilization markers would be a useful adjunct to improving understanding of this process. Until such research is done, clinicians must be aware of the possible embryocidal mechanisms of action of hormonal contraceptive methods. Regardless of whether or not a medical professional prescribes hormonal contraceptives, information about the possible embryocidal potential of hormonal contraceptives will be important information for patients who are currently considering or using hormonal contraceptives. For those who do prescribe hormonal contraceptives, this information should be communicated to patients as part of full informed consent.

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